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13. ABSTRACT ***(Maximum 200 Words)***

This project will assess the association between the risk of breast cancer and polymorphisms of the androgen and vitamin D receptor among subjects in a recently-completed population-based case-control study in Sweden. A total of 3879 cases and 3527 controls took part, providing questionnaire data regarding use of exogenous hormones and other life style factors. From this study population, 1800 cases and 1800 controls will be randomly selected for genomic DNA analysis. The collection of blood or tissue specimens for DNA has been funded from other sources; this award is for the measurement of the AR and VDR on 300 cases and 300 controls who never used HRT, and 300 cases and 300 controls who used HRT for 4 years or more. Information on these polymorphisms will be incorporated into the established subject database, and odds ratios summarizing the associations with breast cancer risk will be computed. In the first year of the project, the administrative arrangements for the work were established, and a tracking database for subject recruitment and specimen accrual built. Recruitment into the molecular epidemiology study is proceeding well, and the anticipated laboratory analyses will begin shortly.

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N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

N/A For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

N/A In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

PI - Signature Date

Table of Contents

Introduction

This project aims to assess the association between the risk of breast cancer and polymorphisms of the androgen and vitamin D receptor genes (AR and VDR genes). This will be accomplished in the context of a recently-completed population-based case-control study in Sweden. A total 3879 cases and 3527 controls took part, providing questionnaire data regarding use of exogenous hormones, cigarette smoking, alcohol use, and other life style factors. From this study population, 1800 cases and 1800 controls will be randomly selected for genomic DNA analysis. The collection of blood or tissue specimens for DNA has been funded by other awards (from the National Institutes of Health and from the Army Medical Research and Materiel Command Breast Cancer Research Program). This award is for the measurement of the AR and VDR on 300 cases and 300 controls who never used HRT, and 300 cases and 300 controls who used HRT for 4 years or more. Information on these polymorphisms will be incorporated into the established subject database, and odds ratios summarizing the associations with breast cancer risk will be computed.

Progress to Date

Under previous funding, all questionnaire data have been obtained and organized, and several manuscripts dealing with the questionnaire data have been published:

Magnusson C, Baron JA. Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. International Journal of Cancer. 81(3):339-44, 1999

Magnusson CM, Persson IR, Baron JA, Ekbom A, Bergstrom R. Adami HO. The role of reproductive factors and use of oral contraceptives in the aetiology of breast cancer in women aged 50 to 74 years. International Journal of Cancer. 80(2):231-6, 1999.

Magnusson C. Baron J, Persson I, Wolk A, Bergstrom R, Trichopoulos D, Adami HO. Body size in different periods of life and breast cancer risk in post-menopausal women. International Journal of Cancer. 76(1):29-34, 1998.

Administrative Preliminaries

The grantee organization, Dartmouth College, has established a subcontract with the Karolinska Institutet for the collaborative work described in our proposal. The Karolinska Institutet has an on-going relationship with investigators at Uppsala University in Uppsala, Sweden where most of the molecular analyses will be conducted.

Recontacting study subjects to obtain germline DNA for analyses

This work, still in progress, has been funded by other awards from the National Institutes of Health and from the Army Medical Research and Materiel Command Breast Cancer Research Program. A substantial part of these efforts must be completed before the analyses funded in this project can proceed.

Recontact of cases and controls has proceeded in two phases. In phase I, 1198 subjects were selected. Of these, 918 agreed to donate blood, and 61 living subjects declined to give blood, but allowed use of tissue samples to obtain germline DNA, A further 171 subjects had died, but we will attempt to extract DNA from mastectomy and biopsy tissue samples. Thus we expect to obtain DNA from 1150 (96%) of the case selected. Seventeen further controls are considering whether to take part.

Of the 1112 controls chosen in phase I, 854 (77%) agreed to donate blood samples. 55 controls have died; without mastectomy/biopsy specimens to access, there is no readily available source of germline DNA for these subjects, or for the 228 control subjects who declined to give a blood specimen. To date, we have actually received blood specimens for 904 cases and 831 controls. Efforts continue to obtain blood on those who have agreed.

In the second phase of recruitment for the molecular studies, an additional 600 cases and 600 controls have been selected for recontact. We are in the process of sending out the letters to these women, and enter them into the process of obtaining blood specimens as in Phase I.

An administrative database has been constructed using MS Access to facilitate the in order to track the specimens and prepare for the incorporation of the laboratory results into the analysis database. This database allows us to track specimens in "real time," knowing where each subject stands in the process of recruitment, tissue retrieval and transshipment, and analysis. In addition, the system generates lists of patients to contact, mailing labels, letters, etc.

After being entered into the system, all blood/tissue specimens are sent to the molecular epidemiology laboratory in Uppsala, Sweden. DNA is being extracted, and the assays will begin shortly.

Appendix I

Key Research Accomplishments

- Completion of Organizational Prerequisites
- Construction of a Detailed Administrative Database
- Recruitment of Subjects to Molecular Epidemiology Study

Appendix II

Reportable Outcomes:

(None)